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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,673	01/16/2004	Danila Valmori	LUD 5483.7 DIV (10316191)	7395

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FULBRIGHT & JAWORSKI, LLP
666 FIFTH AVE
NEW YORK, NY 10103-3198

EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	**PAPER NUMBER**
1644	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,673	VALMORI ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *1/16/04, 2/7/05, 11/2/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-23* is/are pending in the application.

4a) Of the above claim(s) *23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/16/04 (Fig 1-4), 4/6/04 (Fig 5-7)* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/19/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 1/16/04, Applicant's amendment and response filed 2/7/05, and Applicant's response filed 11/2/06 are acknowledged and have been entered.

2. STIC corrected the following errors in Applicant's CRF filed 2/7/05: with regard to Sequence 2, STIC inserted ending bracket in the <213> numeric identifier, and with regard to Sequence 31, STIC corrected the spelling of "Artificial."

3. Applicant is required under 37 C.F.R. 1.821(d) to amend the specification to list the appropriate SEQ ID NOS for sequences disclosed in the specification (for example, in the Brief Description of the Drawings for Figures 2 and 4-8 and Tables I-IV on pages 10, 12, 14 and 15, respectively).

4. Applicant's election of Group I, drawn to a method for inducing proliferation of CTL, said method comprising contacting a sample containing CTLp with a polytope, wherein said polytope comprises an amino acid sequence found in a Melan-A molecule and said sequence forms a complex with an HLA class I molecule, and species of SEQ ID NO: 9 in Applicant's response filed 11/2/06 is acknowledged.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP 818.03(a)).

Claims 19-22 read on the elected species, SEQ ID NO: 9.

Accordingly, claim 23 (Invention of Group II) is withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Claims 19-22 are presently being examined as they read on the elected species, SEQ ID NO: 9.

5. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

6. The disclosure is objected to because of the following informalities:

a. There are blank underlined spaces on page 28 at lines 26-30.

b. There are handwritten alterations on pages 15 and 17 of the specification that have not been initialed and dated.

c. The font size used for Table V on page 17 of the specification is too small to be read clearly.

d. " U.S. Patent No. 6,052,470" disclosed on page 1 at line 5 is the wrong patent number. The correct number is U.S. Patent No. 6,025,470.

Appropriate correction(s) is/are required.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 19-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 19 is indefinite in the recitation of "and which forms a complex with an HLA molecule" because it is not clear what is meant, *i.e.,* if the polytope or the amino acid sequence forms a complex with an HLA molecule.

9. For the purpose of prior art rejections, the filing date of the instant claims 19-22 is deemed to be the filing date of the 09/061,388 parent application, *i.e.,* 4/16/98, as the 08/880,963 parent application does not support the claimed limitation "polytope" recited in claims 19 and 22 of the instant application.

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 19-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valmori *et al* (J. Immunol. 160: 1750-1758, 2/98, IDS reference) in view of Gilbert *et al* (Nature Biotech. 1997, 15: 1280-1284) and US Patent No. 5,662,907.

Valmori *et al* teach modified Melan-A peptide analogs that bind to HLA-*0201 and are recognized by TIL and CTL clones when the TIL or CTL clones are mixed with HLA-A*0201 expressing T2 target cells pulsed with the peptides. Valmori *et al* teach the peptide ELAGIGILTV that is SEQ ID NO: 9 of instant claim 22, Applicant's elected species. Valmori *et al* also teach several of Applicant's non-elected species of peptide, *i.e.,* EMAGIGILTV (SEQ ID NO: 10), EALGIGILTV (SEQ ID NO: 11), YAAGIGILTV (SEQ ID NO: 13), FAAGIGILTV (SEQ ID NO: 14), AMGIGILTV (SEQ ID NO: 6), LAGIGLITV (SEQ ID NO: 7), and MAGIGILTV (SEQ ID NO: 8). Valmori *et al* teach that these peptides were designed to overcome the relatively poor binding of natural Melan-A peptides to HLA-A*0201, and that analog peptides with greater immunogenicity than their natural counterparts may be useful in shortening the stimulation time required to obtain the large numbers of peptide-specific effector CTL populations required for adoptive transfer therapy, *i.e.,* for stimulating CTL with peptide in context of stimulator cells bearing HLA-A*0201, and the assessment of the immunogenicity of these analog peptides in HLA-A2/Kb transgenic mice. Valmori *et al* teach that the ELAGIGILTV (SEQ ID NO: 9) decapeptide forms stable complexes with cell-associated HLAA*0201, is recognized more efficiently than the natural decapeptide by TIL and by Melan-A specific CTL clones, and is more efficient than the natural deca- or nona-peptides in inducing melanoma-reactive CTL. Valmori *et al* teach that this peptide analogue could be used as a vaccine able to elicit potent antitumor CTL responses. Valmori *et al* teach the high correlation that has been found between overall peptide affinity for MHC class I and *in vivo* peptide immunogenicity in HLA-A2K^b transgenic mice, and an even better correlation with a peptide's ability to form stable HLA-A2 complexes. Valmori *et al* teach that tumor reactive CTL were induced *in vitro* by stimulation of autologous irradiated PBMC by pulsing with the ELAGIGILTV (SEQ ID NO: 9) peptide analog. Valmori *et al* teach melanoma associated antigens recognized by CTL from cancer patients include peptides from products expressed in some melanomas as well as in subsets of different human tumor types, but not in normal tissues except testis and placenta, such as MAGE, from mutant proteins, or from melanocyte lineage-specific antigens such as tyrosinase, ap100, gp75 and Melan-A/MART-1 (see entire reference, especially Abstract, Results and Discussion sections).

Valmori *et al* do not teach the claimed method wherein the Melan-A analog peptide is in the form of a polytope, nor do Valmori *et al* explicitly teach that in adoptive therapy CTL the stimulating peptides are added to cells that present HLA molecules on their surface.

Gilbert *et al* teach constructing polytope proteins comprising one or more class I MHC-restricted CTL epitopes and the p1 protein of the retrotransposon Ty1 of *S. cerevisiae*, and optionally also comprising CD4 epitopes. Gilbert *et al* teach that their polytope protein consists of a single protein species that can be simply produced in yeast at high yields and carries a string of up to 15 defined CTL epitopes from *Plasmodium* species, said polytope protein effectively primes protective CTL responses in mice following a single administration without adjuvant. Gilbert *et al* teach that effective processing of epitopes from the string was demonstrated *in vitro* and *in vivo* and was not affected by flanking sequences. Gilbert *et al* teach that using minimal epitopes to produce vaccines instead of whole antigens enables the immune response to be directed towards conserved regions of antigens. Gilbert *et al* teach that in mice, the response towards the polyepitope protein is long lasting and can be boosted, that in humans they are safe and elicit cellular and proliferative responses to the vaccine. Gilbert *et al* teach that in humans, use of alum adjuvant impairs CTL response, but in a phase I trial where no adjuvant was used, CTL responses were induced to the polyepitope protein (see entire article, especially abstract, introduction, discussion).

US Patent No. 5,662,907 discloses contacting CTL with an immunogenic peptide *in vitro* and then reintroducing the activated cells into a patient with cancer, such as melanoma, or that alternatively, the peptides can be used as a vaccine to induce an immune response *in vivo*, or a combination of both methods may be used. US Patent No. 5,662,907 discloses that the peptides may be used therapeutically to elicit CTL responses to melanoma in the form of a peptidic vaccine, or for *ex vivo* therapy in which CTL are induced in tissue culture and used for adoptive immunotherapy. US Patent No. 5,662,907 discloses that *ex vivo* CTL responses to a tumor antigen are induced by incubating in tissue culture the patient's CTL precursor cells together with a source of antigen presenting cells (APC) and the appropriate immunogenic peptide. US Patent No. 5,662,907 discloses using more than one peptide in a vaccine or using heteropolymers of different peptides for stimulating CTL responses for the advantage of increased immunological reaction and the additional ability to induce CTL that react with different antigenic determinant of the tumor cells, and different types of APC, including autologous PBMC, pAPC such as dendritic cells and activated B cells (especially column 2 at lines 26-33, column 4 at lines 8-16, column 12 at lines 13-44, column 13 at lines 19-37).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a vaccine composition containing the ELAGIGILTV analog peptide taught by Valmori *et al* in the form of a polyepitope (*i.e.*, polytope) peptide as taught by Gilbert *et al* or as disclosed by US Patent No. 5,662,907, either in combination with other Melan-A analog peptides taught by Vamori *et al* or with other melanoma tumor associated antigenic peptides such as those disclosed by US Patent No. 5,662,907, and to have used the polytope peptide to stimulate CTLp *in vitro* using APC expressing the HLA-A*0201 restriction element taught by Valmori *et al* or disclosed

by US Patent No. 5,662,907 in the method of stimulating CTLp *ex vivo* taught by Valmori *et al* or disclosed by US Patent No. 5,662,907.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to expand CTLp for adoptive therapy as taught by Valmori *et al* and disclosed by US Patent No. 5,662,907 as a modality for treating melanoma as disclosed by US Patent No. 5,662,907 or as taught by Valmori *et al*, because Valmori *et al* teach that the ELAGIGILTV analog peptide may be used in a vaccine, both Gilbert *et al* teach and US Patent No. 5,662,907 discloses the advantages of using a polytope vaccine over a single epitope vaccine and Valmori *et al* teach several more of the analog peptides formed stable complexes with HLA-A*0201 and were recognized by TIL or CTL. One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make CTL for the adoptive therapy component of the combination therapy disclosed by US Patent No. 5,662,907 of using both *ex vivo* stimulated CTL and the peptide vaccine, and because US Patent No. 5,662,907 discloses using more than one peptide in a vaccine in the form a heteropolymer of active peptide units for the advantage of an increased immune response and reactivity against more than one antigenic determinant on a tumor cell.

12. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

13. Claims 19-22 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,326,200 in view of Gilbert *et al* (Nature Biotech. 1997, 15: 1280-1284) and US Patent No. 5,662,907.

Claims 1-4 of U.S. Patent No. 6,326,200 recite a method for provoking proliferation of CTL comprising contacting a sample containing CTLp with a complex of a peptide and an HLA-A2 molecule, wherein the sequence of the peptide is an amino acid sequence found in Melan-A that is one of SEQ ID NO: 13-15 (that are identical to SEQ ID NO: 13-15 recited in instant claim 22).

Claims 1-4 of U.S. Patent No. 6,326,200 do not recite that the method comprises contacting the CTLp with a polytope, wherein said polytope comprises an amino acid sequence found in Melan-A, including SEQ ID NO: 13-15 recited in instant claim 22, and a sample of cells which present HLA molecules on their surfaces and which process said polytope to Melan-A peptides that complex with said HLA molecules, including wherein the HLA molecule is HLA-A2 recited in instant claim 21.

Gilbert *et al* teach constructing polytope proteins comprising one or more class I MHC-restricted CTL epitopes and the p1 protein of the retrotransposon Ty1 of *S. cerevisiae*, and optionally also comprising CD4 epitopes. Gilbert *et al* teach that their polytope protein consists of a single protein species that can be simply produced in yeast at high yields and carries a string of up to 15 defined CTL epitopes from *Plasmodium* species, said polytope protein effectively primes protective CTL responses in mice following a single administration without adjuvant. Gilbert *et al* teach that effective processing of epitopes from the string was demonstrated *in vitro* and *in vivo* and was not affected by flanking sequences. Gilbert *et al* teach that using minimal epitopes to produce vaccines instead of whole antigens enables the immune response to be directed towards conserved regions of antigens. Gilbert *et al* teach that in mice, the response towards the polyepitope protein is long lasting and can be boosted, that in humans they are safe and elicit cellular and proliferative responses to the vaccine. Gilbert *et al* teach that in humans, use of alum adjuvant impairs CTL response, but in a phase I trial where no adjuvant was used, CTL responses were induced to the polyepitope protein (see entire article, especially abstract, introduction, discussion).

US Patent No. 5,662,907 discloses contacting CTL with an immunogenic peptide *in vitro* and then reintroducing the activated cells into a patient with cancer, such as melanoma, or that alternatively, the peptides can be used as a vaccine to induce an immune response *in vivo*, or a combination of both methods may be used. US Patent No. 5,662,907 discloses that the peptides may be used therapeutically to elicit CTL responses to melanoma in the form of a peptidic vaccine, or for *ex vivo* therapy in which CTL are induced in tissue culture and used for adoptive immunotherapy. US Patent No. 5,662,907 discloses that *ex vivo* CTL responses to a tumor antigen are induced by incubating in tissue culture the patient's CTL precursor cells together with a source of antigen presenting cells (APC) and the appropriate immunogenic peptide. US Patent

No. 5,662,907 discloses using more than one peptide in a vaccine or using heteropolymers of different peptides for stimulating CTL responses for the advantage of increased immunological reaction and the additional ability to induce CTL that react with different antigenic determinant of the tumor cells, and different types of APC, including autologous PBMC, pAPC such as dendritic cells and activated B cells (especially column 2 at lines 26-33, column 4 at lines 8-16, column 12 at lines 13-44, column 13 at lines 19-37).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made and used a polytope such as taught by Gilbert *et al* and disclosed by US Patent No. 5,662,907 in the method of claims 1-4 of '200, *i.e,* to have made a complex of the peptide and HLA-A2 using a polytope peptide that would be processed to form the said complex.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to stimulate CTLp *ex vivo* as disclosed by US Patent No. 5,662,907 using a polyepitope peptide with multiple CTL epitopes taught by both references to be advantageous in increased immune response with multiple CTL specificities to tumor antigens, and for generating CTL *ex vivo* for adoptive immunotherapy or the combination therapy disclosed by US Patent No. 5,662,907.

14. No claim is allowed.

15. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marianne DiBrino, Ph.D.
Patent Examiner
Group 1640
Technology Center 1600
January 17, 2007

CHRISTINA CHAN
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600